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NIXON & VANDERHYE, PC			EXAMINER	
901 NORTH GLEBE ROAD, 11TH FLOOR			RAMIREZ, DELIA M	
ARLINGTON, VA 22203				
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/538,000	<b>Applicant(s)</b> PLOMP ET AL.
	<b>Examiner</b> DELIA M. RAMIREZ	<b>Art Unit</b> 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) Responsive to communication(s) filed on 12 January 2009.

2a) This action is FINAL.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4) Claim(s) 1-11, 14-29 and 32-36 is/are pending in the application.

4a) Of the above claim(s) 1-11, 14-21, 26-29, 35 and 36 is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 22-25 and 32-34 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All    b) Some \* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 1/12/09/6/29/05.

4) Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.

5) Notice of Informal Patent Application

6) Other: alignments abstract.

**DETAILED ACTION**

***Status of the Application***

Claims 1-11, 14-29, 32-36 are pending.

Applicant's election with traverse of Group IV, claims 22-25, 32, drawn in part to the asparaginase of SEQ ID NO: 3 as submitted in a communication filed on 1/12/2009 is acknowledged.

Applicant's amendment of claims 11, 22, 24, 26, cancellation of claims 12-13, 30-31, and addition of claims 33-36 as submitted in a communication filed on 1/12/2009 is acknowledged.

Applicant's traverse is on the ground(s) that examination of all the inventions would not constitute a serious burden on the Office. Applicant's arguments have been fully considered but are not deemed persuasive to withdraw the restriction requirement. As stated by the Examiner in the restriction requirement mailed on 10/10/2008, the claimed inventions were found not so linked as to form a single general inventive concept under PCT Rule 13.1. While lack of unity and not burden of search has been the basis for the restriction requirement imposed by the Examiner in the instant application, it is noted that contrary to Applicant's assertions, a comprehensive search of all the inventions would require sequence, patent/non-patent literature, as well as class/subclass searches which may not be co-extensive, therefore imposing an undue burden on the Office.

The requirement is deemed proper and therefore is made FINAL.

New claims 33-34 are directed to the elected subject matter. New claims 35-36 are drawn to non-elected subject matter, i.e., a method of manufacturing the polypeptide of claim 26. Claims 1-11, 14-21, 26-29, 35-36 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 22-25 and 32-34 are at issue and are being examined herein.

***Specification***

1. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See, particularly, page 10, lines 5, 12, 16, 30. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.
2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The current title is directed to a novel food production process. However the claimed invention is a polypeptide. Appropriate correction is required.

***Priority***

3. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to EUROPEAN PATENT OFFICE application 02102819.6 filed on 12/19/2002. The foreign priority document is in English.
4. This application is the US National stage of PCT/EP03/14553 filed on 12/18/2003.
5. The protein of SEQ ID NO: 3 was first disclosed in PCT/EP03/14553.

***Information Disclosure Statement***

6. The information disclosure statements (IDS) submitted on 6/29/2005 and 1/12/2009 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

***Claim Objections***

7. Claim 24 is objected to because it refers to a non-elected claim, i.e., claim 11. For examination purposes, it will be assumed that claim 24 is an independent claim which recites the relevant portions of claim 11 associated with the claimed subject matter. Appropriate correction is required.

8. Claims 23, 32-34 are objected to due to the recitation of “An....asparaginase according to claim X”. The claims should be amended to recite “The ....asparaginase according to claim X” because the asparaginase has already been defined in claim X. Appropriate correction is required.

9. Claim 25 is objected to due to the recitation of “recombinant asparaginase comprising...”. To be consistent with commonly used claim language, it is suggested the term be amended to recite “a recombinant asparaginase comprising...”. Appropriate correction is required.

***Claim Rejections - 35 USC § 112, Second Paragraph***

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claim 25 is indefinite in the recitation of “asparaginase comprising a functional domain of any of the asparaginase according to claim 22” for the following reasons. It is unclear as to what is encompassed by a functional domain in view of the fact that a protein can have many functions. For example, a protein can have enzymatic activity as well as being able to elicit an immunological response. Therefore, since one cannot determine which is the intended function, one cannot determine which domain is that comprised by the asparaginase. For examination purposes, it will be assumed that the claim is directed to any asparaginase which comprises any fragment of a polypeptide which is 80% sequence identical to the polypeptide of SEQ ID NO: 3. If the intended function is the enzymatic function, it is suggested the term

be amended to recite, for example, “a recombinant asparaginase comprising an enzymatically active fragment of the asparaginase of claim 22”. Correction is required.

***Claim Rejections - 35 USC § 112, First Paragraph***

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 23, 24, 25, 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 23 is directed in part to a genus of asparaginases having at least 80% sequence identity to the polypeptide of SEQ ID NO: 3 wherein said asparaginases are obtained from *A. niger*. Claims 24 and 32 are directed in part to a genus of asparaginases which are encoded by polynucleotides which may or may not hybridize to the polynucleotides of SEQ ID NO: 1 or 2 under the conditions recited in claim 11.

Claim 25 is directed in part to a genus of asparaginases comprising any fragment of an asparaginase which has at least 80% sequence identity to the polypeptide of SEQ ID NO: 3. See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation. It is noted that the term “hybridisable” means “can hybridize”. As such, the polynucleotide recited in claim 11 is not required to hybridize under the conditions recited to the polynucleotides of SEQ ID NO: 1 or 2, consequently a protein encoded by such polynucleotide is not required to share any structural feature with the polypeptide of SEQ ID NO: 3. Similarly, the asparaginase of claim 25 does not have to share any structural feature with the polypeptide of SEQ ID NO: 3 in view of the fact that a fragment of a polypeptide which is 80% sequence identical to

SEQ ID NO: 3 can be a fragment from a portion of the protein which shares no structural feature with the polypeptide of SEQ ID NO: 3.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that “A written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials”. As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

While the specification in the instant application discloses the structure of a single species of the recited genus of proteins having asparaginase activity and obtained from *A. niger*, i.e., the polypeptide of SEQ ID NO: 3, it provides no clue as to the structural elements required in any asparaginase which is at least 80% sequence identical to the polypeptide of SEQ ID NO: 3 that are characteristic of asparaginases from *A. niger* not found in asparaginases from other sources. Furthermore, the specification does not provide the structural elements required in any asparaginase, nor does it teach which are the structural features within SEQ ID NO: 3 that are required in any protein having asparaginase activity. A structure/function correlation which would allow one of skill in the art to envision the entire structure of any asparaginase or any *A. niger* asparaginase has not been disclosed in the specification or the prior art.

There is no teaching in the specification and/or the prior art indicating the level of structural similarity among asparaginases from *A. niger* with respect to the polypeptide of SEQ ID NO: 3, nor is there any teaching or suggestion that all *A. niger* asparaginases will have a sequence identity of at least 80% with respect to the polypeptide of SEQ ID NO: 3.

With regard to claims 24-25, 32, the claims encompass proteins sharing no structural features. A sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by their amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, there is no recited structural feature or a known correlation between structure and function which would provide the structural features common to all members of the genus. In addition, while one could argue that SEQ ID NO: 3 is representative of the structure of all the members of the genus, such that the recited genus of polypeptides is adequately described by the disclosure of the structure of the polypeptide of SEQ ID NO: 3, it is noted that the art teaches several examples of how even small variations in structure can lead to changes in function. For example, Witkowsky et al. (Biochemistry 38:11643-11650, 1999) teach that one conservative amino acid substitution transforms a  $\beta$ -ketoacyl synthase into a malonyl decarboxylase and completely eliminates  $\beta$ -ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teach that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since minor structural changes to a polypeptide may result in changes affecting function, and no additional information correlating structure with the activity has been provided, one cannot reasonably conclude that SEQ ID NO: 3 is representative of the structure of all proteins having the recited asparaginase activity encompassed by the claims.

Due to the fact that the specification only discloses a single species of the genus, i.e. the polypeptide of SEQ ID NO: 3, and the lack of description of any additional species by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

15. Claims 22-25, 32-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the asparaginase of SEQ ID NO: 3, does not reasonably provide enablement for (a) an asparaginase which is at least 80% sequence identical to the polypeptide of SEQ ID NO: 3, (b) an asparaginase which comprises any fragment of (a), or (c) any asparaginase encoded by a polynucleotide which may or may not hybridize to the polynucleotide of SEQ ID NO: 1 or 2 under the recited conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

***The breadth of the claims.*** Claims 22-25, 32-33 are so broad as to encompass (a) any asparaginase which is at least 80% sequence identical to the polypeptide of SEQ ID NO: 3, (b) any asparaginase which comprises any fragment of (a), and (c) any asparaginase encoded by a polynucleotide which may or may not hybridize to the polynucleotide of SEQ ID NO: 1 or 2 under the recited

conditions. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation. It is noted that claim 23 encompasses not only asparaginases from *A. niger* but it also encompasses any asparaginase which is at least 80% sequence identical to the polypeptide of SEQ ID NO: 3 in view of the fact that the term "obtainable" means "can be obtained", thus there is no requirement that the asparaginase of claim 23 must be from *A. niger*. Also, as extensively discussed above, the asparaginases of claims 24-25 and 32 do not have to share any structural feature with the polypeptide of SEQ ID NO: 3. The enablement provided is not commensurate in scope with the claim due to the extremely large number of proteins of unknown structure encompassed by the claim. In the instant case, the specification enables a single species, i.e., the polypeptide of SEQ ID NO: 3.

*The amount of direction or guidance presented and the existence of working examples.* The specification discloses the amino acid sequence of a single protein as a working example (SEQ ID NO: 3). However, the specification fails to provide any clue as to the structural elements required in any protein having asparaginase activity, or which are the structural elements in the polypeptide of SEQ ID NO: 3 which are essential for any protein to display asparaginase activity. No correlation between structure and function has been presented. There is no information or guidance as to which amino acid residues in the polypeptide of SEQ ID NO: 3 can be modified and which ones are to be conserved to create a variant as claimed displaying the same activity as that of the polypeptide of SEQ ID NO: 3.

*The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art.* The amino acid sequence of a polypeptide determines its structural and functional properties. While the art discloses several proteins having asparaginase activity, neither the specification nor the art provide a correlation between structure and asparaginase activity such that one of skill in the art can envision the structure of any protein having asparaginase activity. In addition, the art does not provide any teaching or guidance as to (1) which changes can be made to the protein of SEQ ID NO: 3 such that the resulting variant would display asparaginase activity, or (2) the general tolerance of

Art Unit: 1652

asparaginases to structural modifications and the extent of such tolerance. The art clearly teaches that modification of a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are tolerant of modification and which ones are conserved is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

*The quantity of experimentation required to practice the claimed invention based on the teachings of the specification.* While methods of generating or isolating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for an essentially infinite number of polypeptides and determine which ones have asparaginase activity. The total number of variants of a polypeptide having a specific sequence identity can be calculated from the formula  $N! \times 19^A / (N-A)! / A!$ , where N is the length in amino acids of the reference polypeptide and A is the number of allowed substitutions for a specific % identity. Thus, for a variant of the polypeptide of SEQ ID NO: 3 having 80% sequence identity to SEQ ID NO: 3, the total number of variants to be tested is  $378! \times 19^{76} / (378-76)! / 76!$  (SEQ ID NO:3 has 378 amino acids; 76 amino acids =  $0.2 \times 378$ ) or  $1.91 \times 10^{178}$  variants. While enablement is not precluded by the necessity for routine screening,

if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In the absence of (1) a rational and predictable scheme for modifying any residue in the polypeptide of SEQ ID NO: 3 such that the resulting variant would maintain asparaginase activity, and/or (2) a correlation between structure and asparaginase activity, one of skill in the art would have to test an essentially infinite number of proteins to determine which ones have asparaginase activity.

Therefore, taking into consideration the extremely broad scope of the claim, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and the desired function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

*Claim Rejections - 35 USC § 102*

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 22-25, 32-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Louboudy S. (Egyptian Journal of Biotechnology 4:110-123, 1998). Claims 22-25, 32-34 are directed in part to an asparaginase isolated from *A. niger* which comprises SEQ ID NO:3. It is noted that even if one were to interpret the term "obtainable" as "obtained", the limitations in claims 24 and 32 regarding how to obtain

the asparaginase or the host cell used to recombinantly produce the asparaginase are limitations associated with the manufacture of the asparaginase. The patentability of a product recited in a product-by-process format is determined only by the characteristics of the product (MPEP § 2113). Louboudy teaches the isolation and purification of an L-asparaginase from *A. niger* which is most active in the presence of buffers having a pH range of 6-6.6 (citrate-containing buffers) and is active within a temperature range of 22-45 C (Abstract). The specification of the instant application discloses that the polypeptide of SEQ ID NO:3 is from *A. niger* and that it prefers acidic conditions (Table 3). The polypeptide of SEQ ID NO: 3 is enzymatically active at least at 37 C (Example 3). While Louboudy does not teach the amino acid sequence of his asparaginase, the amino acid sequence of a protein is simply another characteristic of a protein. Since the source of the asparaginase is the same and the asparaginase of Louboudy and the asparaginase of SEQ ID NO: 3 are enzymatically active at the same pH and temperature ranges, in the absence of evidence to the contrary, the asparaginase of Louboudy et al. anticipates the instant claims as written.

18. Claims 24-25, 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Minton et al. (PIR accession number A26064, 1999). Claims 24-25 and 32 are directed in part to any asparaginase. As indicated above with regard to claims 24 and 32, the patentability of a product recited in a product-by-process format is determined only by the characteristics of the product (MPEP § 2113). Also, as indicated above, claims 24-25 and 32 are directed to any asparaginase in view of the fact that (1) the term "obtainable" means "can be obtained", thus the asparaginase does not have to be encoded by the polynucleotide recited in claim 11, and (2) an asparaginase which comprises any fragment of a polypeptide having at least 80% sequence identity to the polypeptide of SEQ ID NO: 3 can be an asparagine which comprises a portion of the 80% sequence identity variant which shares no structural features with the polypeptide of SEQ ID NO: 3. See extensive discussion of scope in Claim Rejections

Art Unit: 1652

under 112, first paragraph. Minton et al. teach an asparaginase which is 43.1% sequence identical to the polypeptide of SEQ ID NO: 3 (163 matches; 43.1 % = 100x163/378) and comprises several fragments of the polypeptide of SEQ ID NO: 3. Therefore, the polypeptide of Minton et al. anticipates the instant claims as written.

***Conclusion***

19. No claim is in condition for allowance.

20. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (571) 273-8300. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (sec 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

21. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez, Ph.D., whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 9:30:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashaat Nashed can be reached on (571) 272-0934. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Primary Patent Examiner  
Art Unit 1652

DR  
April 1, 2009